REMARKS/ARGUMENTS

In order to expedite prosecution, the subject matter of claims 4, 6 (in full) plus 9 and 10 (in part) has been cognated into amended claim 1. Claims 4 and 6 have consequently been cancelled. Claims 2-3, 5, and 7-15 have been amended.

1. CLAIM REJECTIONS: 35 USC §103

Claims 1 to 15 stand rejected as being unpatentable over Griffiths (WO 03/059397) in view of the combination of Yngve [Int.Diss.Abs., 62 (2001)] and Bottcher (US 5,439,863), and in further view of Maier-Borst (GB 2056471 A).

The instant invention concerns coordination chemistry, the chemistry of complex compounds made up of a metal ion and surrounded by ligands. In particular it relates to coordination metal complexes of the radioactive isotopes of gallium and their use as radiopharmaceuticals for diagnostic imaging *in vivo*. Bottcher, on the other hand, concerns non-radioactive metal complexes as "latent polymerization catalysts" (abstract of Bottcher). Bottcher uses macroscopic, in fact molar amounts (1 to 2 moles) of metal ion in Examples 1 to 4 therein, and envisages that the metal complexes would precipitate as crystals (Column 3 lines 38-50 and Column 6 lines 3-8 of Bottcher).

Such macroscopic scale, indeed crystallization, represents completely different chemistry to the high dilution solutions employed with the radioisotopes of the present invention. Thus, applicants contend that the person skilled in the art would know that such radiometal complexes are rarely if ever handled in macroscopic amounts, but instead used in microscopic chemical quantities in solution. That in turn typically means using very small

volumes of solution (in the range μL to a few cm^3). Thus, radioactive gallium complexes are typically prepared in nanomolar amounts. That represents a dilution factor of 10^6 to 10^9 compared to Bottcher. Such use of high dilution techniques is partly due to safety considerations (elevated radiation dose risk due to the more concentrated emissions), but also due to self-radiolysis of the compound in question. Radiolysis refers to decomposition of the compound induced by radioactive emissions, and the person skilled in the art would know that high concentrations of radioactivity (let alone isolated solids) would be highly susceptible to self-radiolysis.. That is due to the very high radioactive concentration and consequent very high intensity of radioactive emissions.

Moreover, the instant invention deals with macromolecular bioconjugates, i.e. "bifunctional chelates" (see present specification at page 6 line 13 to page 7 line 11). Bottcher does not teach, disclose, or suggest the use of macromolecular bioconjugates. Unlike the present invention, Bottcher studies the preparation of metal complex salts of second and third group metals and multidentate chelating agents. The instant application, however, focuses on gallium radioisotopes [as Ga(III)] complexation with macrocyclic chelators – particularly conjugated to "targeting vectors" (claim 7). Appellants contend that the person skilled in the art would know that such vectors are typically expected to be particularly sensitive to radiolysis, and hence would simply be unsuitable for the robust chemical conditions taught by Bottcher. Thus, Bottcher and Griffiths are in very different fields of endeavor. Appellants therefore contend that the person skilled in the art could have no motivation to combine Griffiths and Bottcher.

Applicants also wish to point out that "the prior art itself must provide a motivation or reason for the worker in the art, without the benefit of the Applicant's specification, to make necessary changes in the reference device". See, *Ex parte Chicago Rawhide Manufacturing Co.*, 226 U.S.P.Q. 438 (PTO Bd. App. 1984). Bottcher only teaches the use of metal complex salts of second and third group metals and multidentate chelating agents and is silent on: gallium; radiometals in general; ^{68}Ga in particular; and bifunctional chelates.

Additionally, there is no teaching in Bottcher of successfully applying microwave activation in coordination chemistry. The Examiner asserts out on page 4 of the final Office Action dated April 03, 2009 that "Bottcher *et al*....discloses the preparation of metal complex salts *via* microwave irradiation (column 3, line 45)".

Applicants respectfully disagree with that analysis. Bottcher (Column 3 lines 38-49) states that a high energy input using high shear forces (eg. high stirrer speed) is advantageous, and suggests that "...ultrasound, microwaves or laser beam could also provide the energy input. Bottcher does not, however, provide any supporting Examples where microwave energy is actually used, i.e. shown to be beneficial. Thus, Examples 1, 3 and 4 therein use high speed stirring, and Example 2 ultrasound. Accordingly, Applicants respectfully submit that a vision is not the legal standard to apply when ascertaining whether a prior art reference is obvious over an invention. For these reasons also, applicants contend that the person skilled in the art could have no motivation to combine Griffiths and Bottcher.

Finally, Bottcher is silent on the specific microwave conditions of present, revised claim 1 – where the irradiation power and time are specified. No combination of [Griffiths and Bottcher] could therefore provide the subject matter of revised claim 1.

In view of the foregoing, it is respectfully submitted that the 35 U.S.C. §103 rejections of claims 1-15 over Griffiths in view of Bottcher be withdrawn.

Yngve and Maier-Borst are silent on the use of microwave irradiation in the preparation of radioactive gallium complexes. Hence, those two references cannot remedy the deficiencies of [Griffiths and Bottcher]. Claim 1 is therefore believed non-obvious over the combination of Griffiths plus Bottcher with either or both of Yngve and Maier-Borst. By definition, the same logic applies to dependent claims 2, 3, 5 and 7 to 15.

The Examiner's logic is apparently that present claim 1 is obvious over [Griffiths and Bottcher] and that the additional features of claim 11 could be obtained in an obvious manner from Maier-Borst (GB 2056471 A). That logic is no longer valid since, as argued above, [Griffiths and Bottcher] does not provide the subject matter of present revised claim 1. Consequently the combination [Griffiths and Bottcher and Maier-Borst] does not provide all the essential features of present claim 11. The obviousness rejection in that regard should therefore also be withdrawn.

Yngve describes the preparation of ^{68}Ga-DOTA-oligonucleotide complexes, where ^{68}Ga is obtained *via* an ion exchange column. Yngve is, however, silent on microwave irradiation.

Yngve cannot therefore remedy the deficiencies of [Griffiths and Bottcher] or [Griffiths and Bottcher and Maier-Borst]. All claims are therefore believed non-obvious, over that combination. The obviousness rejection based on Yngve should therefore also be withdrawn.

2. Double Patenting.

Claims 1, 3-7 and 15 are provisionally rejected in this regard over corresponding application USSN 10/552206.

Claims 1-14 are provisionally rejected in this regard over corresponding application USSN 111/358681.

Applicants will file a suitable terminal disclaimer in the event that this application is deemed allowable.

3. Claim Objection.

Claim 1 has been amended by deleting the phrase "and wherein the." found at the end of the claim.

CONCLUSION

In view of the amendments and remarks herein, Applicants believe that each ground for rejection made in the present application has been successfully overcome, and that all the pending claims, 1-15, are in condition for allowance.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

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